Environmental Tobacco Smoke Exposure and Asthma in Adults

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Environmental tobacco smoke (ETS) contaminates indoor air in homes and workplaces. Although the adverse effects of active cigarette smoking on the respiratory tract have been extensively characterized, the effects of ETS exposure on adult asthma have not yet been investigated extensively and the available data are limited. This article examines the evidence for ETS exposure as a cause of asthma and asthma exacerbation in adults, and for ETS exposure in the workplace specifically as contributing to these health effects. It addresses methodological barriers that limit the available data and evaluates the adequacy of the data for risk assessment. *Key words*: airway reactivity, asthma, environmental tobacco smoke, passive smoking. — *Environ Health Perspect* 107(suppl 6):891–895 (1999).
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This article addresses the relevant data on the relationship of environmental tobacco smoke (ETS) exposure to asthma in adults. The studies considered in this review were identified through a comprehensive literature search strategy as well as through recent comprehensive summaries of the literature, including the 1997 report of the California Environmental Protection Agency (*1*) and other reviews (*2,3*).

Specific questions to be considered include *a*) whether there are data supporting ETS as a cause of asthma in adults and if there is information specifically related to workplace exposure, and *b*) whether there are data indicating that ETS exposure is associated with exacerbations of asthma in adults. These questions represent an appropriate starting point for determining if the data are sufficient for a quantitative risk assessment to be conducted on the effects of workplace exposure to ETS on asthma in adults. There is substantial literature on particulate air pollution and asthma but primarily concerning children (*4–6*). This literature may also prove informative as additional studies are reported, particularly of adults with asthma. Additionally, evidence elsewhere in the literature (*1,7*) strongly links childhood exposure to ETS with asthma exacerbation in children and provides some evidence that ETS increases risk for the incidence of asthma.

Before considering the two questions, we describe the natural history of asthma as a disease and also briefly consider the role of active cigarette smoking and its relationship to asthma. The topic of asthma and ETS has been recently reviewed in the 1997 report of the California Environmental Protection Agency on ETS (*1*) and by Coultas (*8*) in 1998.

Natural History of Asthma

Asthma is primarily a disease with its origins in childhood (*9*). Half of all asthma is diagnosed by 3 years of age and 80% by 6 years of age (*10*). However, in many children, symptoms lessen with age, and many no longer carry the diagnosis of asthma as they move into the teen and young adult years (*11*). Estimates suggest that 30–50% of all asthma with onset in childhood becomes asymptomatic by early adulthood, and not all wheezing illnesses in childhood reflect the presence of underlying asthma (*11*). Factors associated with persistence of disease include female gender, degree of atopy or allergic predisposition, and severity of symptoms. Given this background, a large percentage of individuals entering early adult life have various features of the asthmatic predisposition but may not have evidence of active clinical disease. For example, they may manifest skin test reactivity to common allergens at higher levels of total serum IgE or asymptomatic increases in nonspecific airways responsiveness.

There are some incident cases of asthma in adults, and the incidence of asthma begins to rise with age from the young adult years (*9*). Occupational exposures account for some cases, but the etiology of asthma in adults has received little investigation. Identifying persons with onset of asthma during adulthood may be difficult because many persons with an intermediate phenotype—that is, displaying some features of asthma but not carrying a clinical diagnosis—may have had childhood asthma, now forgotten. They may be unaware of their earlier symptoms and illness history. Thus, recall bias may influence the apparent clinical expression of disease in adult life. A variety of factors (allergen exposure, viral respiratory illness, air pollution, and active and passive cigarette smoking) may result in enough symptoms in an adult, formerly diagnosed with childhood asthma, to again pass the clinical threshold for a diagnosis. Because of faulty recollection of prior asthma, recrudescence of symptoms in adults may be interpreted as incidence of disease. Consequently, distinguishing onset of asthma in adulthood from recrudescence of childhood asthma may be difficult. Whether the distinction is directly relevant to preventing asthma in adults is unclear. For this review, we consider persons with asthma as potentially susceptible to ETS exposure, whether the asthma was incident in childhood or adulthood.

An additional methodological concern in interpreting the evidence on active and passive smoking and asthma is introduced by a form of selection bias that has been referred to as the healthy smoker effect (*12*). This bias refers to the self-selection of persons with better respiratory health to be active smokers compared with those who remain nonsmokers. This form of bias may well apply to persons with childhood asthma. The degree to which asthmatic individuals in childhood have more severe symptoms and more severe disease may influence their probability of becoming active smokers; individuals who have greater levels of airways responsiveness or are very symptomatic may be less likely to become regular cigarette smokers. The resulting bias or healthy smoker effect will tend to obscure associations between active smoking and asthma, particularly in cross-sectional studies. This same type of bias may extend to cross-sectional studies of persons exposed to ETS, who may choose to avoid exposure to ETS, depending on their underlying state of respiratory health.

The available evidence shows that increased airways responsiveness does determine susceptibility to the harmful effects of active cigarette smoking, both in

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cross-sectional and longitudinal data, the latter providing stronger support for this self-selection (*13*). The bulk of the cross-sectional data would support a relationship between smoking and increased levels of airways responsiveness despite the potential for selection bias in the studies (*12*). However, with regard to an association of active smoking with asthma, the cross-sectional data are more equivocal. Cross-sectional studies, which are again subject to potential selection bias, have yielded both positive (*14*) and negative results (*15–17*). Longitudinal data, which are less subject to the potential of selection bias, are unequivocal in supporting a role of active smoking in asthma occurrence (*18,19*).

Evidence indicates that an association of active smoking with asthma is biologically plausible. Active cigarette smoke exposure is associated with airways inflammation, increased levels of peripheral blood neutrophils and eosinophils, increased levels of airways responsiveness, airway wall remodeling, increased levels of total IgE, and inflammation of the small airways (*20*), all indicators of biologic effects consistent with the development of asthma and its intermediate phenotypes. In addition, longitudinal data, particularly those from the landmark longitudinal study of Fletcher and Peto (*21*) and the Lung Health Study (*13*), clearly support asthma or airways responsiveness as defining susceptibility to active cigarette smoking and accelerated decline of lung function. With this background, we turn to the two critical questions with regard to ETS and asthma.

The Role of ETS in Causing Asthma in Adults

Several studies have examined the role of ETS exposure as a potential causative factor for asthma in adults. Two prospective cohort studies have assessed risk factors for incident asthma. Hu and colleagues (*22*) investigated risk factors for incident asthma in a group of young adults who had been participants in a cross-sectional survey that assessed passive smoking exposure at home. Survey participants were asked to report on a physician's diagnosis of asthma and on symptoms and medications for those having asthma. Parental smoking had been recorded in an earlier survey of the same group, carried out when the participants were in the seventh grade. At 20–22 years of age, parental smoking was a risk factor for having physician-diagnosed asthma (odds ratio [OR] = 2.9, 95% confidence interval [CI]: 1.6, 5.6) and current asthma (OR = 3.3; 95% CI: 1.7, 6.4).

In a study of 3,914 Seventh Day Adventists, primarily nonsmokers, workplace exposure to ETS was a risk factor for incident asthma over a 10-year interval that began at a mean age of 56.5 years (*23*). In this study, Greer and colleagues tracked the development of respiratory symptoms and diseases by administering a standardized respiratory questionnaire at the start and end of the follow-up interval. Incident asthma cases were identified as a new report of a diagnosis and related symptoms. In a multiple logistic regression model, workplace exposure to ETS through 1987 (estimated using "years worked with a smoker") was significantly associated with 10-year cumulative incidence; the estimated increase for 10 years exposure = 1.45 (95% CI: 1.21–1.80). In this study, exposure to ETS was reported on the follow-up questionnaire and the possibility of differential reporting of ETS exposure should be considered. Persons developing asthma may have been more likely to notice and report exposure than those not developing asthma.

Flodin and co-workers (*24*) conducted a population-based case–control study based in the geographic region of Southern Sweden. The investigators used a very strict definition of asthma that included age of onset greater than age 20 years, documented evidence of methacholine responsiveness, or an increase of > 15% in FEV_1 (forced expiratory volume in 1 sec) with a bronchodilator and respiratory symptoms consistent with asthma. ETS exposure was assessed both at home and at work through use of a questionnaire. Only 29 of the 79 adult onset asthmatic cases were ex-smokers for whom smoking had ended at least 1 year before onset of asthma. The data clearly document that ever smoking, particularly ex-smoking, was associated with the development of asthma in adults (OR = 3.3, 95% CI: 1.8–6.0). A total of 61 of the 79 asthmatic subjects were exposed to passive smoking, 35 at work and 26 at home. The odds ratio for exposure for passive smoking at work in relation to an asthma diagnosis was 1.5 (95% CI: 0.8–2.5).

This is a relatively small case–control study that may, in fact, underestimate the effect of active cigarette smoking as a risk factor for asthma. Recall bias, both in terms of timing of disease onset and exposure assessment, is a potential problem in this study. Given the limited statistical power, the finding that the odds ratio for passive smoking is not significant at $p < 0.05$ is not surprising. Interpreting the magnitude of effect is also limited by the sample size, as the odds ratios are imprecisely estimated. With this constraint, the point estimate for the effect of passive smoking is about half that of active smoking. The relative similarity of the effects of active and passive smoking does not seem consistent with the relative doses of tobacco smoke associated with the two exposures. Although, the nonsignificant results might be predicted from the small sample size, the study data do suggest that workplace exposure, particularly as assessed in this study with four different exposure categories, may affect the risk of asthma in the adult population.

The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) (*25*) also addressed ETS exposure and asthma in adults. The SAPALDIA study is a cross-sectional, multicity study conducted in Switzerland that included 4,197 nonsmoking adults between the ages of 18 and 60 years. Asthma was defined in the standard manner by the American Thoracic Society - Division of Lung Diseases questionnaire as a self-report of a doctor's diagnosis. Never smokers were persons who never smoked or smoked less than 20 pack years in their lifetime, whereas passive smokers were described as individuals who were exposed to ETS for the past 12 months. Workplace exposure was assessed, both as the number of smokers to whom the respondent was exposed and as the number of hours per day of exposure. An exhaled CO determination was performed to assess exposure misclassification. Seventy percent of males and 52% of females reported ETS exposure. ETS exposure was associated with an increased risk of asthma as well as wheezing apart from colds, dyspnea on exertion, bronchitis episodes, and chronic bronchitis symptoms. The risk for asthma increased with the number of smokers to which the respondent was exposed and the number of hours per day, but no additional risk was associated with workplace exposure versus home exposure. Adjustment for a variety of confounding variables, including passive smoking exposure in childhood, education, occupation, gender, and city did not change the results for ETS overall. For workplace ETS exposure, the risk was greater for wheezing (OR = 2.05; 95% CI: 1.46–2.92), dyspnea (OR = 1.62; 95% CI: 1.29–2.03), symptoms of chronic bronchitis (OR = 1.66, 95% CI: 1.18–2.33), and bronchitis symptoms (OR = 1.67, 95% CI: 1.23–2.28) (*25*).

These studies have differing designs—cross-sectional, cohort, and case–control—but their findings provide an indication of potential effects of ETS exposure in the workplace on persons with asthma. Their results may be subject to the complex biases considered above—both selection bias and both differential and nondifferential misclassification of exposure. They highlight the difficulty and challenge of accurately assessing workplace exposure and of interpreting findings that may be subject to selection bias that cannot be characterized readily. In summary, at present there are limited epidemiologic data on the relationship of ETS exposure as a cause of adult asthma.

ETS Exposure as an Exacerbating Factor for Asthma in Adults: Epidemiologic Evidence

Only a few observational studies have been reported. These studies have used self-report of exposure, which is potentially subject to information bias. On days with greater severity of symptoms, for example, persons with asthma may be more likely to notice exposure to ETS in the microenvironments where they spend time.

In a study carried out in India by Jindal and colleagues (*26*), 200 persons with asthma were evaluated, 100 never smokers with ETS exposure and 100 never smokers without ETS exposure. The definition of never smoker was not clearly given in the report. Asthma was defined as a physician's diagnosis with the presence of variable airflow obstruction. The design of this study incorporated an ETS exposure questionnaire that assessed the hours per day exposed to ETS for the past year along with emergency room visits, hospitalization, acute episodes, requirement of parenteral drugs at home, corticosteroids, and maintenance bronchodilators during the same time period. ETS exposure was considered to be present if exposure was greater than or equal to 1 hr/day or at least 7 hr/week based on the questionnaire. Outcomes included emergency room visits, hospitalizations, exacerbations of asthma, medication use, and absences from work. The ETS-exposed asthmatics retrospectively reported greater emergency room visits, hospitalizations, medication use, and absence from work when compared to the non-ETS exposed asthmatic subjects.

This report is potentially subject to selection bias regarding the types of clinical asthmatics selected and also to the possibility of recall bias in terms of exposure assessment and health outcomes. In addition, the exposure assessment did not differentiate workplace and home exposure to ETS. Consequently, these positive findings need cautious interpretation.

In a panel study of 164 adults with asthma in Denver, Colorado, Ostro et al. (*27*) recorded symptoms, medications, and exposures to indoor pollutants on a daily basis. ETS exposure at home was assessed for each day by self-report. Exposure to ETS was associated with increased risk for a number of symptoms and with restriction in activity. Report of ETS exposure was associated with increased risk for moderate or severe cough (OR = 1.21; 95% CI: 1.01–1.46), moderate or severe shortness of breath (OR = 1.85; 95% CI: 1.57–2.18), nocturnal asthma (OR = 1.24; 95% CI 1.00–1.53), and restricted activity (OR = 2.08; 95% CI: 1.63–2.64). Workplace exposures were not assessed in this study.

ETS Exposure as an Exacerbating Factor for Asthma in Adults: Evidence from Controlled Exposure Studies

By necessity, clinical studies—exposures of volunteers to pollutants with intensive assessment of responses—assess acute responses to pollutants. An important feature of the controlled clinical study is the opportunity to examine both healthy volunteers and individuals with underlying cardiopulmonary diseases such as asthma. Subjects are typically classified by age, gender, race, and lung function. Asthmatics are often characterized by their responsiveness to methacholine or histamine, presence or absence of allergy (skin tests or IgE levels), use of medication, severity of symptoms, and degree of airway obstruction assessed by pulmonary function tests. Typically, persons who are healthy or have only mild asthma tend to volunteer for clinical protocols, whereas more severely obstructed asthmatics are usually not included.

A variety of studies (Table 1) have reported on short-term exposures of asthmatics to ETS generated by smoking machines in environmental chambers. Of course, by design, participants cannot be blinded to being exposed to ETS because of its characteristic odor. Brief exposure to ETS produces symptoms such as eye and nasopharyngeal irritation, with much less consistent responses in lung function measures. In general, the experimental studies show that brief exposure to ETS produces symptoms such as eye and nasopharyngeal irritation, with much less consistent responses in lung function measures (Table 1). Early clinical studies focused on changes in pulmonary mechanics resulting from 1- to 2-hr exposures (*28,29*). For example, Dahms and colleagues (*29*) observed a mean decrease in FEV_1 and FVC (forced vital capacity) of 20% following a 1-hr ETS exposure while asking participants not to take bronchodilators in the few hours before exposure. In contrast, Shephard et al. (*28*) observed no change in lung function following a 2-hr exposure but allowed volunteers to use their asthma medications prior to exposure. Other features of protocol design, including subject's atopic status, history of recent respiratory infections, or differences in ETS concentration or exposure duration could influence lung function.

In subsequent studies, the measurement of airway reactivity after pollutant exposure to increasing doses of a known bronchoconstricting agent such as methacholine was introduced into protocol design. This approach was incorporated into several studies but also yielded inconsistent results as studies demonstrated increased reactivity (*30–32*), no change in reactivity (*33,34*) or a decrease in reactivity (*35*). Although a few studies showed adverse effects of exposure on function, the majority documented no significant effect on FEV_1 or measures of airway responsiveness.

Because many patients with bronchial asthma spontaneously report respiratory symptoms during or immediately after exposure to ETS, a relationship between ETS-induced symptoms, airway caliber, and airway responsiveness is plausible. Indeed, Stankus et al. (*36*) investigated the effects of a 2-hr exposure to ETS in 21 subjects with asthma who previously claimed respiratory symptoms from ETS exposure. In 7 of these 21 subjects, a fall in FEV_1 of > 20% was found. These findings suggest that there might be a subgroup of smoke-sensitive asthmatic subjects who develop acute airway obstruction after breathing ETS. A subsequent study by this group (*32*) partially confirmed the observation; 5 of 31 sensitive subjects with asthma and none of 39 smoke-sensitive subjects without asthma reacted to cigarette-smoke challenge with a > 20% fall from baseline FEV_1. However, a history of symptoms induced by ETS has not been a consistently reproducible marker of pulmonary responsiveness to ETS. For example, Jorres and Magnussen (*33*) exposed a group of 24 asthmatics, 16 of whom had a history of passive smoke-induced respiratory symptoms, to ETS for 1 hr. ETS-induced symptoms could not be predicted from the history of passive smoke-related complaints. Airway responsiveness to methacholine, as estimated from spirometric or body plethysmographic measurements, was not influenced by the ETS challenge. In contrast to Stankus and colleagues (*36*), Jorres and Magnussen concluded that respiratory symptoms in smoke-sensitive subjects are unlikely to be based on airway obstruction.

Several factors might have led to the largely negative findings. Duration exposure was generally brief, lasting 1 to 2 hr; exposures of longer duration or multiple, intermittent exposures as occur in the workplace may have enhanced airway responsiveness. Small sample sizes in most clinical studies constrain interpretation of the data. Often there was a wide variability in responses among ETS-exposed asthmatics (*37*), which may in part reflect differences in subject characteristics and exposure protocols: obstructed versus nonobstructed asthmatics, smoke-sensitive versus smoke-insensitive asthmatics, and subject requirements for medication. Undoubtedly, factors in subject selection also affect responsiveness in clinical studies. Not only the selection criteria per se but the subject's environment is probably of importance. For example, subjects living in highly

polluted urban areas are perhaps less responsive (i.e., more tolerant) than those coming from less polluted environments. Identification of factors that predispose to ETS responsiveness requires further investigation. However, it is notable that asthmatics who responded to ETS on an initial exposure responded on a second exposure 2 years later (*31*). In addition, Menon and colleagues (*31*) found that pretreatment with albuterol or cromolyn can protect against ETS-induced airway reactivity. Perhaps protection by antioxidants accounts for some of the variability of the ETS-induced responses. Finally, Nowak and colleagues (*37*) observed that the nocturnal decrease in FEV_1 was more pronounced after ETS than after sham; this observation may be important for patients with bronchial asthma, for whom one of the features is nocturnal impairment of lung function.

The evidence on short-term effects of ETS on asthma is inconclusive but cannot be ignored. Controlled studies of acute exposure of asthmatics to ETS have generated conflicting data, yet there is evidence that individual asthmatics and groups of asthmatics do respond to levels of ETS that do not elicit responses in healthy volunteers. Additionally, these studies are limited in duration and do not replicate a typical day's exposure. Important dimensions of study design worthy of consideration include using exposures of longer duration, sequential exposures over several days, and better characterization of the asthmatic population. It is noteworthy that a 3-hr exposure of mild asthmatics to ETS was insufficient to invoke an inflammatory response in nasal or bronchoalveolar lavage fluid (*38*).

Conclusions

On the basis of the above review, it appears that there are only scant data assessing the role for ETS exposure in adult asthma. There is some evidence that ETS exposure in general, and especially ETS exposure in the workplace, contributes to both development and exacerbation of asthma. However, because of a limited number of studies and potential problems in their design, definitive conclusions cannot be made at this time. Data from volunteer studies and exposure chamber studies are consistent with the epidemiologic data but do not, in and of themselves, consistently support the relationship between ETS exposure and adult asthma.

Table 1. Pulmonary effects of ETS in asthmatics.

Investigator	Design	Exposure	Findings	Comments
Shephard et al., 1979 (*28*)	14 asthmatics inhaled ETS for 2 hr in closed room	Smoking machine Particles = 2–4 mg/m^3 CO = 24 ppm	No change in lung function; few changes in symptoms	Air control exposure
Dahms et al., 1981 (*29*)	10 asthmatics inhaled ETS for 1 hr in a chamber	Smoking machine COHb increased 0.4%	Decrease in FEV_1 and FVC of 20%	No change in lung function of control subjects; no sham exposure
Knight and Breslin, 1985 (*30*)	6 asthmatics inhaled ETS for 1 hr in a room; bronchoconstrictor response to histamine	Smoke produced mechanically	Increased symptoms; decrease in FEV_1 and PC_{20}	Air control exposure
Wiedemann et al., 1986 (*35*)	9 asthmatics inhaled ETS for 1 hr in a chamber; bronchoconstrictor response to methacholine	Smoking machine CO = 40–50 ppm	No change in lung function; decrease in airway reactivity	No control exposure; significance of decrease in airway reactivity unclear
Stankus et al., 1988 (*36*)	21 smoke-sensitive asthmatics inhaled ETS for 2 hr at 2 levels in a chamber	Smoking machine CO = 9 ppm; 13 ppm Particles = 0.9; 1.4 mg/m^3 Nicotine = 0.2; 0.4 mg/m^3	No apparent group effect on lung function	7/21 subjects experienced > 20% fall in FEV_1; no control exposure
Menon et al., 1991 (*31*)	15 atopic smoke-sensitive asthmatics inhaled ETS for 2–6 hr in a chamber; bronchoconstrictor response to methacholine	Smoking machine Particles = 1.1 mg/m^3 Nicotine = 0.2 mg/m^3	5/6 asthmatics known reactors 24 months previously had > 20% fall in FEV_1 after 2-hr exposure; 9 nonreactors remained nonreactive with 6-hr exposure	Pretreatment with medication decreased airway reactivity to ETS
Jorres and Magnussen, 1992 (*33*)	24 asthmatics inhaled ETS for 1 hr in a chamber; bronchoconstrictor response to methacholine	Smoking machine CO = 20 ppm Particles = 3.1 mg/m^3 Nicotine = 0.3 mg/m^3	No significant effect on lung function or airway responsiveness; eye and nasopharyngeal irritation	Cross-over with air; smoke-sensitive asthmatics not more responsive
Magnussen et al., 1992 (*34*)	18 adult and 11 childhood asthmatics for 1 hr in a chamber; bronchoconstrictor response to methacholine or histamine	Smoking machine CO = 21 ppm Particles = 2.7 mg/m^3 Nicotine = 0.4 mg/m^3	No change in lung function or airway responsiveness; eye and nasopharyngeal irritation	Cross-over with air
Menon et al., 1992 (*32*)	31 smoke-sensitive asthmatics inhaled ETS for 2–6 hr in a chamber; bronchoconstrictor response to methacholine	Smoking machine Particles = 1.3 mg/m^3 Nicotine = 0.2 mg/m^3	1/3 of smoke-sensitive group increased reactivity 6-hr post-exposure	Heterogeneous response and duration of response; no control exposure
Danuser et al., 1993 (*39*)	10 individuals with airway hyperreactivity to methacholine and respiratory symptoms inhaled ETS	2-min provocation test with increasing CO concentration (0, 2, 4, 8, 16, 32 ppm)	Significant decrease in FEV_1, FVC, and MEF_{50}	Decrease most pronounced after the lowest dose of 2 ppm
Nowak et al., 1997 (*38*)	17 asthmatics inhaled ETS for 3 hr in a chamber in the evening; bronchoconstrictor response to methacholine	Smoking machine CO = 22 ppm Particles = 3.2 mg/m^3	Nocturnal decrease in FEV greater after ETS than sham; no effect on airway responsiveness	Wide interindividual variability; cross-over with air
Nowak et al., 1997 (*37*)	10 asthmatics inhaled ETS in a chamber in the evening	Smoking machine CO = 22 ppm Particles = 3.2 mg/m^3	No effect on lung function or cells in BAL or nasal lavage	Cross-over with air

Abbreviations: BAL, bronchoalveolar lavage; MEF_{50}, maximal expiratory flow at 50% of vital capacity; PC_{20}, provocative concentration of histamine causing a 20% decrease in FEV_1.

Thus, ETS exposure has not yet been confirmed as a hazard for adults with asthma. Given the importance of this issue, there is a strong rationale for additional epidemiologic studies of ETS in the indoor environment. Clinical studies have the potential to be informative about the effects of ETS but require careful attention to protocol design and they cannot be blinded as to the exposure.

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